Title: *FOXP2*-Related Speech and Language Disorders *GeneReview* – Neuroimaging Findings
Authors: Morgan A, Fisher SE, Scheffer I, Hildebrand M
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Detailed Information on Neuroimaging Findings in the KE Family with a *FOXP2*-Only-Related Disorder

In the KE family with a *FOXP2*-only-related disorder [see Vargha-Khadem et al 2005 for review], atypical brain structure or function has been revealed by voxel-based morphometry (VBM) and functional imaging methods as outlined below. It is not known, however, whether other individuals with a *FOXP2*-only-related disorder or a *FOXP2*-plus-related disorder share neurologic findings similar to these, as no other studies exist in this area. Hence, the following information is provided more as important background to the condition and its likely mechanistic pathways between genes-brain-behavior but it is arguably too early to use these neuroimaging findings as clinical markers of *FOXP2*-related speech and language disorders.

Brain morphology in affected compared to unaffected KE family members using VBM revealed less grey matter density, or morphologic anomalies, bilaterally in key cortical and subcortical regions including the head of the caudate nucleus, inferior frontal gyrus (Broca's area), the precentral gyrus, the temporal pole, and the ventral cerebellum [Belton et al 2003]. Further anomalies were characterized by increases in grey matter density in the posterior part of the superior temporal gyrus (Wernicke's area), the angular gyrus, and the putamen [Belton et al 2003]. A volumetry study using VBM data also showed reduced volume bilaterally in the caudate nucleus of affected family members compared to unaffected members and age- and sex-matched controls [Watkins et al 2002]. Taken together, these MRI findings are also in agreement with independent gene expression studies of *FOXP2* in the brain of the human embryo and *Foxp2* in the mouse, which highlight the same structures [Lai et al 2003].

A number of functional brain activation studies have also been conducted on the KE family. The first was a positron emission tomography study that found functional anomalies of the caudate nucleus that also correlated with speech outcome [Vargha-Khadem et al 1998]. Later, task-related functional MRI (fMRI) studies were conducted [Liégeois et al 2003]. The first fMRI study compared brain activation for affected and unaffected KE family members on three different tasks, specifically: silent verb generation, spoken verb generation, and word repetition [Liégeois et al 2003]. Overall, fMRI findings revealed under-activation in affected relative to unaffected KE members in the putamen, Broca's area, and the right hemisphere homolog of Broca's region [Liégeois et al 2003]. A more recent task-related fMRI study in the KE family required affected members and healthy control participants to produce non-words aloud in the scanner [Liégeois et al 2011]. Not only did the affected family members perform poorly on the non-word repetition task in the scanner relative to controls, but brain activation was also significantly reduced in the premotor, supplementary and primary motor

cortices as well as in the basal ganglia and cerebellum. That is, the findings implicated similar regions to those previously reported to be functionally abnormal in the KE family [Liégeois et al 2003]. Because of the striking difference in performance between affected and unaffected members on this task and because the task recruits brain regions involved in the imitation and vocal learning of novel sequences of speech sounds, non-word repetition fMRI was proposed by the authors to be the optimal endophenotype for indexing *FOXP2* disruption in humans [Liégeois et al 2011].

In summary, findings from the KE family suggest that mutation of *FOXP2* is associated with anomalies in cortical (primary motor cortex, inferior frontal gyrus, posterior superior temporal gyrus), subcortical (caudate nucleus, putamen) and white-matter 'language tracts' [Watkins et al 2002, Belton et al 2003, Liégeois et al 2003, Liégeois et al 2011]. It appears that the *FOXP2* pathogenic variant in affected KE family members has thus disrupted both the structure and function of brain regions involved in auditory-motor integration, speech learning, planning/programming, and execution of speech. These neural changes are in turn associated with a chronic speech and language disorder – predominantly manifesting as CAS [Morgan et al 2010].

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